

University of Dundee

## Hormone replacement therapy for women with type 1 diabetes mellitus

Mackay, Liz; Kilbride, Lynn; Adamson, Karen A.; Chisholm, John

*Published in:*  
Cochrane Database of Systematic Reviews

*DOI:*  
[10.1002/14651858.CD008613.pub2](https://doi.org/10.1002/14651858.CD008613.pub2)

*Publication date:*  
2013

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

*Citation for published version (APA):*  
Mackay, L., Kilbride, L., Adamson, K. A., & Chisholm, J. (2013). Hormone replacement therapy for women with type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews*, (6), 1-22. [CD008613].  
<https://doi.org/10.1002/14651858.CD008613.pub2>

### General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.



**Cochrane**  
**Library**

**Cochrane** Database of Systematic Reviews

## **Hormone replacement therapy for women with type 1 diabetes mellitus (Review)**

Mackay L, Kilbride L, Adamson KA, Chisholm J

Mackay L, Kilbride L, Adamson KA, Chisholm J.

Hormone replacement therapy for women with type 1 diabetes mellitus.

*Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD008613.

DOI: 10.1002/14651858.CD008613.pub2.

**[www.cochranelibrary.com](http://www.cochranelibrary.com)**

## TABLE OF CONTENTS

HEADER . . . . .	1
ABSTRACT . . . . .	1
PLAIN LANGUAGE SUMMARY . . . . .	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . . .	3
BACKGROUND . . . . .	4
OBJECTIVES . . . . .	6
METHODS . . . . .	6
Figure 1. . . . .	8
RESULTS . . . . .	10
DISCUSSION . . . . .	11
AUTHORS' CONCLUSIONS . . . . .	11
ACKNOWLEDGEMENTS . . . . .	11
REFERENCES . . . . .	12
CHARACTERISTICS OF STUDIES . . . . .	14
DATA AND ANALYSES . . . . .	17
ADDITIONAL TABLES . . . . .	17
APPENDICES . . . . .	17
CONTRIBUTIONS OF AUTHORS . . . . .	22
DECLARATIONS OF INTEREST . . . . .	22
INDEX TERMS . . . . .	22

# Hormone replacement therapy for women with type 1 diabetes mellitus

Liz Mackay<sup>1</sup>, Lynn Kilbride<sup>2</sup>, Karen A Adamson<sup>3</sup>, John Chisholm<sup>4</sup>

<sup>1</sup>Metabolic Unit, Western General Hospital Edinburgh, Edinburgh, UK. <sup>2</sup>School of Nursing, Midwifery and Social Care, Faculty of Health, Life & Social Sciences, Edinburgh Napier University, Edinburgh, UK. <sup>3</sup>Medical Unit, St John's Hospital, Livingston, UK. <sup>4</sup>School of Nursing, Midwifery and Social Care, Edinburgh, Napier University, Edinburgh, UK

Contact address: Liz Mackay, Metabolic Unit, Western General Hospital Edinburgh, Crewe Road, Edinburgh, Lothian, EH4 2XU, UK. [Liz.mackay@luht.scot.nhs.uk](mailto:Liz.mackay@luht.scot.nhs.uk).

**Editorial group:** Cochrane Metabolic and Endocrine Disorders Group.

**Publication status and date:** New, published in Issue 6, 2013.

**Citation:** Mackay L, Kilbride L, Adamson KA, Chisholm J. Hormone replacement therapy for women with type 1 diabetes mellitus. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD008613. DOI: 10.1002/14651858.CD008613.pub2.

Copyright © 2013 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## ABSTRACT

### Background

There is conflicting information about the impact of the menopause on glycaemic control amongst women with type 1 diabetes. Some menopausal women with type 1 diabetes are treated with hormone replacement therapy (HRT) but the effects of this treatment have, to date, not been established.

### Objectives

To assess the effects of HRT for women with type 1 diabetes mellitus.

### Search methods

We searched *The Cochrane Library*, MEDLINE, EMBASE, CINAHL and PsycINFO from their inception to June 2012. The last search was run for all databases on 18 June 2012.

### Selection criteria

We selected randomised controlled trials or controlled clinical trials that involved peri- or postmenopausal women with type 1 diabetes undergoing HRT as an intervention.

### Data collection and analysis

Two researchers independently applied the inclusion criteria to the identified studies and assessed risk of bias. Disagreements were resolved by discussion or by intervention by a third party. Descriptive analysis was conducted for the review.

### Main results

Ninety-two publications were screened. No studies met the inclusion criteria exclusively but one study that included both type 1 and type 2 diabetes participants was considered. This randomised clinical trial (RCT) compared HRT (N = 27) with placebo (N = 29) over 12 months. The outcome measures were cardiovascular risk factors, including lipid profile, glycaemic control, blood pressure and body weight. No significant differences between placebo and HTR were detected. Patient-important outcomes like all-cause mortality, cardiovascular disease, diabetic complications or health-related quality of life were not investigated.

## **Authors' conclusions**

There is a lack of evidence around the use of HRT in women with type 1 diabetes. The one study that has been undertaken in this area is underpowered. More RCTs are required in the area to examine the impact of HRT on glycaemic control and cardiovascular outcomes.

## **PLAIN LANGUAGE SUMMARY**

### **Hormone replacement therapy for women with type 1 diabetes mellitus**

There are increasing numbers of people living with type 1 diabetes mellitus. The main aim of treatment for diabetes is to maintain good quality of life and to minimise, or prevent, the development of diabetic complications by controlling blood glucose levels. Women with type 1 diabetes frequently express difficulties in controlling their blood glucose levels during the menopausal phase of their lives. However, the cause of this has not been explored.

Hormone replacement therapy is a treatment that is prescribed to many women to alleviate the symptoms associated with the menopause.

The literature surrounding hormone replacement therapy and type 1 diabetes has never been systematically searched and reviewed.

The evidence available for healthcare professionals to call upon relating to the management of menopausal women with type 1 diabetes is vague. There is conflicting literature regarding the use of hormone replacement therapy in women with type 1 diabetes, as many of the studies also included women with type 2 diabetes. We found one study with a type 1 diabetes subgroup involving 56 participants receiving either hormone replacement therapy or placebo over 12 months. No statistically significant differences were found between hormone replacement therapy and placebo. Patient-important outcomes like death from any cause, cardiovascular disease (for example, heart attack, stroke), diabetic complications (for example, diabetic eye disease, diabetic kidney disease) or health-related quality of life were not investigated.

## SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [\[Explanation\]](#)

Hormone replacement therapy compared with placebo for women with type 1 diabetes mellitus			
<b>Patient or population:</b> peri- or postmenopausal women with type 1 diabetes mellitus <b>Settings:</b> outpatients <b>Intervention:</b> hormone replacement therapy ((oestrogen (17B-oestradiol, 2 mg) and progesterone (norethisterone acetate, 1 mg)) <b>Comparison:</b> placebo			
Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
Diabetes and non-diabetes related morbidity	See comment	See comment	Not investigated
Death from any cause	See comment	See comment	Not investigated
Adverse effects [follow-up: 12 months]	56 (1)	⊕○○○ <b>very low<sup>a</sup></b>	Most frequently reported event was breast pain (37 type 1 diabetes mellitus and type 2 diabetes mellitus participants on hormone replacement therapy (HRT) versus nine placebo participants); vaginal bleeding occurred in 26 HRT versus three placebo participants
Health-related quality of life	See comment	See comment	Not investigated
Glycaemic control (fructosamine levels) [follow-up: 12 months]	56 (1)	⊕○○○ <b>very low<sup>a</sup></b>	No statistically significant differences between intervention and comparator groups
Economic data	See comment	See comment	Not investigated
GRADE Working Group grades of evidence <b>High quality:</b> Further research is very unlikely to change our confidence in the estimate of effect. <b>Moderate quality:</b> Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. <b>Low quality:</b> Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. <b>Very low quality:</b> We are very uncertain about the estimate.			

<sup>a</sup>Due to very serious indirectness, serious risk of bias, low number of participants and studies

## BACKGROUND

### Description of the condition

Diabetes mellitus is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. A consequence of this is chronic hyperglycaemia (that is elevated levels of plasma glucose) with disturbances of carbohydrate, fat and protein metabolism. Long-term complications of diabetes mellitus include retinopathy, nephropathy and neuropathy. The risk of cardiovascular disease and cancer is increased.

It is acknowledged that there is an increasing number of people who suffer from type 1 diabetes (Diabetes UK 2006). The main aims of treatment for type 1 diabetes are to maintain good health-related quality of life and to minimise, or prevent, the microvascular and macrovascular complications caused by the disease through good glycaemic control (Norris 2001; Signuroardottir 2005). A major trial has demonstrated conclusively that optimal glycaemic control can improve the physical and psychological well-being of people with type 1 diabetes (DCCT 1993). Physiological changes like pregnancy, weight gain, puberty and psychological issues like stress are known to affect glycaemic control (Russel 2001; Weinger 2001). It is well recognised that changes in sex hormones can increase insulin resistance during puberty and pregnancy (Dahlgren 2006). These findings imply that during the menopause a woman's requirement for insulin will be altered.

The menopause is a stage in the female reproductive cycle that occurs as the ovaries stop producing oestrogen causing the reproductive system to cease functioning (Freeman 2007). As the body adapts to changing levels of natural hormones various symptoms may be experienced. These include amongst others: (1) hot flushes, palpitations, night sweats, (2) mood swings, lack of concentration, (3) vaginal dryness, decreased libido, (4) weight changes. To overcome some of these symptoms hormone replacement therapy (HRT) can be prescribed. There is emerging evidence about the benefits and disadvantages of HRT in women with type 1 diabetes (Andersson 2000; Smith 2000). Insulin resistance can be modified by HRT but to date much of the evidence relating to HRT in diabetes has been extrapolated from non-diabetic women. There is some evidence that women with diabetes have a blunted response to the beneficial effects of HRT on lipids (Robinson 1996). Women with diabetes are at increased risk of cardiovascular disease with the pathogenesis linked to insulin resistance (Satter 1996). Interestingly, HRT has been found to be prescribed less in women with diabetes than in women without diabetes (Progetto Menopausa Italia Study Group 2001). However, no link has been found between the use of HRT and mortality in a longitudinal study of women with diabetes in the US (Klein 1999), while there is a suggestion that glycosylated haemoglobin may be significantly decreased in women with type 2 diabetes who take postmenopausal oestrogen (Brussaard 1992).

The experience and management of the menopause amongst women is unique and at times complex. It is proposed that for women with type 1 diabetes managing the menopause is more complex due to changes in their physical and psychological status impacting on their glycaemic control. These women usually have an earlier onset of menopause than women without diabetes (Zarzycki 2005). From practice it is known that often women confuse the signs of the menopause with hypoglycaemia. Both of these physiological changes can result in night sweats, mood changes and palpitations; therefore, it is difficult for the women to distinguish whether they are suffering from hypoglycaemia or experiencing menopausal symptoms. Interestingly, clinical experience suggests that menopausal women are sometimes inappropriately treating their perceived hypoglycaemic symptoms resulting in hyperglycaemia.

Additionally, some people are administering HRT to alleviate symptoms of the menopause but the effectiveness of this intervention has not been clearly established. In addition to the signs and symptoms of the menopause being confused by women with the symptoms of hypoglycaemia causing possible inappropriate insulin use, alterations in diet, weight and mood sometimes experienced during the menopause can also necessitate changes in insulin use. Overall, this can necessitate women to alter their self-management regimen significantly which can cause further physical and psychological stress.

The evidence available to patients and healthcare professionals surrounding the management of menopausal women with type 1 diabetes and health-related quality of life issues is vague. There is conflicting literature surrounding the use of HRT in women with type 1 diabetes and this literature has never been systematically searched, retrieved and reviewed.

### Description of the intervention

The intervention under investigation is HRT versus no hormone therapy in women with type 1 diabetes.

For many years, oestrogen alone or in combination with progestogens, otherwise known as HRT, has been the treatment of choice for control of problematic menopausal symptoms and for the prevention of osteoporosis. A recent publication from the International Menopause Society 2008 has stated that HRT remains the first-line and most effective treatment for menopausal symptoms. The use of HRT in all women has declined after the publication of several studies which linked the treatment to increased risk of breast cancer (Beral 2003; Women's Health Initiative Investigators 2002), coronary heart disease (Women's Health Initiative Investigators 2002) and venous thromboembolism (Hulley 2002).

HRT should currently only be prescribed for menopausal symptoms and not for prevention of osteoporosis or cardiovascular disease. It is currently recommended that the lowest dose of HRT based on relieving menopausal symptoms should be prescribed

([Khoo 2005](#)). Oral HRT regimens are well tolerated and are considered as first-line therapy in most women. There is significant individual variation in response to HRT and it is often appropriate to try two or three different preparations. Women should be encouraged to persevere with a new preparation for two to three months as any side-effects experienced initially may settle with time. Women should be reviewed three months after commencing therapy. The ongoing need for HRT should be reassessed at least annually. Blood pressure should be checked 6 to 12 monthly, and each woman encouraged to attend cervical and breast screening programmes. Breast awareness should be encouraged. Stopping HRT abruptly can cause some women to have hot flushes and it should, therefore, be withdrawn gradually by decreasing dosages over three to six months.

HRT is contra-indicated in the presence of active venous thromboembolism, unexplained vaginal bleeding, oestrogen dependent tumours (breast and endometrial cancer), current or recent cardiovascular disease and acute porphyria. Women who have not had a hysterectomy should be commenced on a sequential or continuous combined form of HRT starting at the lowest dose available and increasing if required to give symptom control. Continuous combined therapy (period-free HRT) should only be used by women who are at least a year past the menopause or over 54 years of age. Both oestrogen and progestogen are taken daily to give a period-free regimen. Erratic bleeding is common in the first few months of use. For women who have had a hysterectomy unopposed oestrogens should be prescribed.

## Possible and known adverse effects of the intervention

### Glycaemic control

Studies have indicated that HRT appears to lower glycaemic control as indicated by glycosylated haemoglobin A1c (HbA1c) in women who have type 2 diabetes. HRT users have a lower than average HbA1c than non-HRT users ([Ferrara 2001](#)). Furthermore, current HRT users may experience better glycaemic control than those who have never used it or who had previously done so ([Crespo 2002](#)). Both these studies indicate that glycaemic control is affected and can be improved in women who have type 2 diabetes taking HRT.

To our knowledge the relationship between HRT and glycaemic control has not been investigated in type 1 diabetes.

### Changes in insulin sensitivity

Studies involving women with type 2 diabetes indicate that oestradiol given orally or transdermally tends to improve insulin sensitivity ([Cagnacci 1992](#)). However, it has also been shown that a dose of 1.25 mg/day reduces insulin sensitivity ([Ajabor 1972](#)). Combining HRT with progestogen may reduce insulin sensitivity ([Lindheim 1993](#)). Furthermore, high doses of approximately 20

mg have no effect on insulin sensitivity, with lower doses of 10 mg/day leading to a decrease in insulin concentrations ([Crook 1997](#)). To our knowledge the relationship between HRT and changes in insulin sensitivity has not been investigated in type 1 diabetes.

### Health-related quality of life

The provision of information, education and psychological support to facilitate self management are essential components of diabetes care and are known to improve health-related quality of life. The interpretation of the data on the effect of HRT on health-related quality of life varies, with the WISDOM study showing measurable improvements in health-related quality of life, sexuality and joint pain in symptomatic women ([Welton 2008](#)); however, women with diabetes were not investigated separately. HRT has been found to be efficacious in comparison with placebo in reducing the frequency and severity of hot flushes in healthy menopausal women ([MacLennan 2004](#)).

### Coronary heart disease (CHD)

The Women's Health Initiative study ([Women's Health Initiative Investigators 2002](#)) showed an increase in CHD events from 30 to 37 cases per 10,000 treated women. However, more recent studies have suggested that HRT does not cause an increase in CHD risk and may have a cardioprotective role in younger women in the early postmenopausal years ([Rossouw 2007](#)). Whether this is the case in women with type 1 diabetes is unclear.

### Venous thromboembolism (VTE)

While the risk of VTE with HRT remains low, a two-fold increase in VTE has been found when standard doses of oral HRT are compared to placebo ([Cushman 2004](#)). Healthy postmenopausal women are at low risk of VTE but the use of HRT is best avoided in women with a previous history of VTE.

### Ovarian cancer

While the Million Women Study collaborators found an increased risk of ovarian cancer in women using HRT compared to women who had never used HRT, the risks were 'small' (one extra case of cancer in 2500 users of HRT) with the risk falling back to pre-use levels when the HRT was discontinued ([Million Women Study Collaborators 2007](#)).

### Breast cancer

The effects of HRT on breast cancer appear to be related to the type of HRT and the duration of the therapy with combined oestrogen and progesterone therapy taken over five years demonstrating the greatest risk. The Women's Health Initiative showed an increase in breast cancer of eight cases per 10,000 treated women ([Women's Health Initiative Investigators 2002](#)).



### Reduced bone mineral density

HRT has a beneficial effect on bone mineral density with the large studies ([Women's Health Initiative Investigators 2002](#)) showing HRT was effective in preventing fractures secondary to osteoporosis.

### Why it is important to do this review

There is currently some ambiguity surrounding the use of HRT in women with type 1 diabetes. The current literature offers conflicting information making clinical decisions problematic. There have been no systematic reviews of the evidence for methods relating to the impact of HRT on menopausal women with type 1 diabetes undertaken to date. This information is necessary to guide professionals when they are considering how best to empower women to manage their diabetes during this stage in their life and also to inform future studies on this group.

## OBJECTIVES

To assess the effects of hormone replacement therapy for women with type 1 diabetes mellitus.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs).

#### Types of participants

Peri- and postmenopausal women with type 1 diabetes.

#### Types of interventions

##### Intervention

- Hormone replacement therapy for women with type 1 diabetes mellitus.

##### Control

- Placebo.
- No intervention.
- Usual care.

### Types of outcome measures

#### Primary outcomes

- Glycaemic control (glycosylated haemoglobin A1c (HbA1c), blood glucose levels (self monitored)).
- Diabetes and non-diabetes related morbidities.
- Health-related quality of life (using validated instruments).

#### Secondary outcomes

- Total daily insulin dosage.
- Body mass index (BMI), weight.
- Frequency and severity of hypoglycaemia.
- Death from any cause.
- Adverse effects.
- Economic data.

#### Covariates, effect modifiers and confounders

- Duration of diabetes.
- Compliance with treatment.
- Diabetes management skills.
- Presence of diabetes complications.
- Age.
- Level of physical activity.

### Timing of outcome measurement

#### *Short term (less than six months)*

- Glycaemic control.
- Total daily insulin dose.
- Diabetes and non-diabetes related morbidities.
- Averse effects.

#### *Medium term (six to 12 months)*

- Diabetes and non-diabetes related morbidities.
- Health-related quality of life.
- Adverse effects.
- BMI, weight or both.

#### *Long term (more than 12 months)*

- Diabetes and non-diabetes related morbidities.
- Adverse effects.
- Death from any cause.
- Economic data.

## Search methods for identification of studies

### Electronic searches

We used the following sources from inception until specified date for the identification of trials.

- *The Cochrane Library* (issue 3, 2012).
- MEDLINE (until June 2012).
- EMBASE (until June 2012).
- CINAHL (until June 2012).
- PsycINFO (until June 2012).

For detailed search strategies please see under [Appendix 1](#).

The ISI Web of Knowledge database was searched for relevant abstracts from conference proceedings. We also searched databases of ongoing trials: 'Current Controlled Trials' ([www.controlled-trials.com](http://www.controlled-trials.com)) - with links to other databases of ongoing trials).

Additional key words of relevance could have been detected during any of the electronic or other searches. In this case, we would have modified electronic search strategies to incorporate these terms. We planned to include studies published in any language.

### Searching other resources

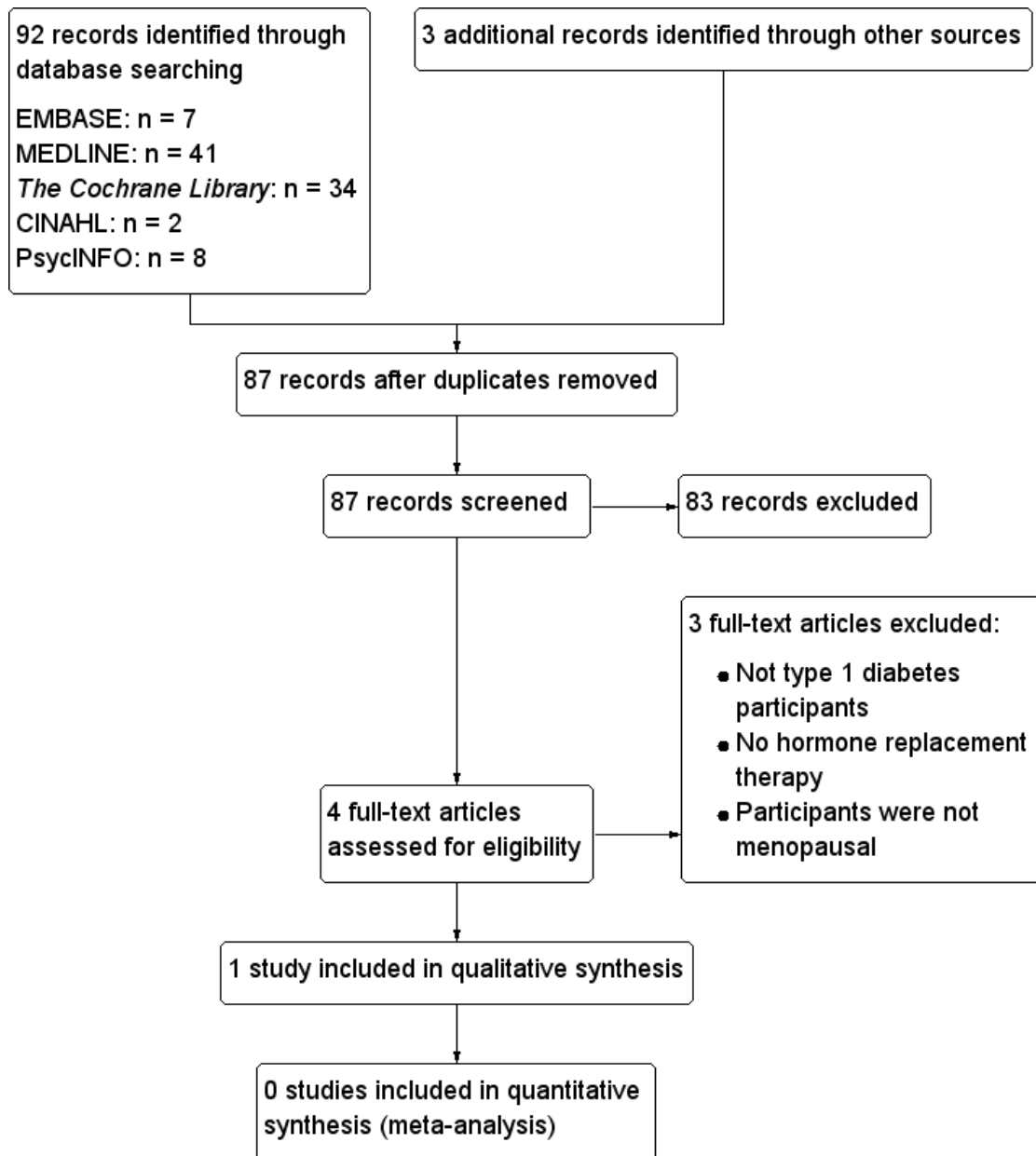
We tried to identify additional studies by searching the reference lists of included trials and systematic reviews, meta-analyses and health technology assessment reports. Potential missing and unpublished studies were sought by contacting expert authors in the field.

## Data collection and analysis

### Selection of studies

To determine the studies to be assessed further, two review authors (LK, JC) independently reviewed the abstracts, title or both sections of every record retrieved. All potentially relevant articles were investigated as full text. Only one study was identified as being suitable for inclusion. An adapted PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow-chart (see [Figure 1](#)) of study selection is attached ([Liberati 2009](#)).

Figure 1. Study flow diagram.



## Data extraction and management

Two review authors (LK, JC) independently abstracted relevant population and intervention characteristics using standard data extraction templates (for details see 'Characteristics of included studies'; Table 1; Appendix 2; Appendix 3; Appendix 4; Appendix 5; Appendix 6) with any disagreements to be resolved by discussion, or if required, by a third party. We sought any relevant missing information on the trial from the original author(s) of the article, if required.

## Assessment of risk of bias in included studies

Two authors (LK, JC) assessed the one trial independently. We assessed risk of bias using The Cochrane Collaboration's tool (Higgins 2011). We used the following criteria.

- Was the allocation sequence adequately generated?
- Was the allocation adequately concealed?
- Was knowledge of the allocated intervention adequately prevented during the study?
- Were incomplete outcome data adequately addressed?
- Were reports of the study free of suggestion of selective outcome reporting?
- Was the study apparently free of other problems that could put it at a high risk of bias?

A judgement of 'Yes' indicates low risk of bias, 'No' indicates high risk of bias and 'Unclear' indicates unclear or unknown risk of bias. We used these criteria for a judgement of 'Yes', 'No' and 'Unclear' for individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to assess the impact of individual bias domains on study results at endpoint and study levels.

## Measures of treatment effect

We planned to express dichotomous data as odds ratios (ORs) or risk ratios (RRs) with 95% confidence intervals (CIs). We planned to express continuous data as mean differences (MD) with 95% CI.

## Unit of analysis issues

We planned to take into account the level at which randomisation occurred, such as cross-over trials, cluster-randomised trials and multiple observations for the same outcome.

## Dealing with missing data

We wanted to obtain relevant missing data from authors, if feasible, and planned to perform evaluation of important numerical data such as screened, randomised patients, as well as intention-to-treat (ITT) and per protocol (PP) populations. We planned to investigate attrition rates, for example, drop-outs, losses to follow-up, withdrawals. We also wanted to critically appraise issues of missing data and techniques to handle these (for example, last-observation-carried-forward (LOCF)).

## Assessment of heterogeneity

In the event of substantial clinical or methodological or statistical heterogeneity we planned not to report study results as meta-analytically pooled effect estimates. We planned to identify heterogeneity by visual inspection of forest plots, by using a standard Chi<sup>2</sup> test and a significance level of  $\alpha = 0.1$ , in view of the low power of this test. We wanted to specifically examine heterogeneity with the I<sup>2</sup> statistic quantifying inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (Higgins 2002), where I<sup>2</sup> values of 50% and more indicates a considerable level of inconsistency (Higgins 2003).

When heterogeneity was found, we planned to determine potential reasons for it by examining individual study and subgroup characteristics.

## Assessment of reporting biases

We planned to use funnel plots to assess for the potential existence of small study bias. There are a number of explanations for the asymmetry of a funnel plot (Sterne 2011). Therefore, we planned to carefully interpret results (Lau 2006).

## Data synthesis

We planned to summarise data statistically if they were available, sufficiently similar and of sufficient quality. We would have performed statistical analyses according to the statistical guidelines referenced in the most recent version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

## Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses and wanted to investigate interaction.

- Post- and perimenopause.
- Type of HRT (oestrogen only, combined oestrogen and progesterone).

## Sensitivity analysis

We planned to perform sensitivity analyses in order to explore the influence of the following factors on effect sizes.

- Restricting the analysis to published studies.
- Restricting the analysis taking into account risk of bias, as specified above.
- Restricting the analysis to very long or large studies to establish how much they dominate the results.
- Restricting the analysis to studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

We also planned to test the robustness of the results by repeating the analysis using different measures of effect size (RR, OR etc.) and different statistical models (fixed-effect and random-effects models).

## RESULTS

### Description of studies

For a detailed description of studies, see Tables 'Characteristics of included studies' and 'Characteristics of excluded studies'.

### Results of the search

The initial search identified 92 records. After removal of duplicates and review of the 87 titles and available abstracts, four potential full text articles and theses were identified for further assessment. Only one study met the inclusion criteria of the review. We excluded the other studies on the basis of their titles or abstracts because they did not meet the inclusion criteria or were not relevant to the question under study or were a duplicate report (see [Figure 1](#) for the amended PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow chart).

### Included studies

The details of the included study ([Scott 2004](#)) are described in the 'Characteristics of included studies' table and appendices. This was a randomised controlled study, although the randomisation process was not stated. Study duration was 12 months.

### Participants and setting

The included study involved postmenopausal women who had type 1 or type 2 diabetes. Stratification was conducted based on the type of diabetes. Both the type 1 (T1DM) and type 2 diabetes (T2DM) groups consisted of a hormone replacement intervention (HRT) and comparator (placebo) arm. After an initial six week run-in period, participants were randomly allocated to HRT or

placebo. Mean age for the HRT group was 60 years and for the placebo group was 59 years. Of the original total (including T1DM and T2DM) of 150 women, 55 withdrew throughout the study, with the main reasons being due to adverse effects or persistence of menopausal symptoms. Data describing the percentage of drop-out relating to type of diabetes were not provided. The included trial's baseline characteristics are stated in [Appendix 3](#).

### Interventions

The intervention group received HRT (oestrogen (17 $\beta$ -oestradiol) and progestogen (norethisterone acetate, 1 mg)), while the placebo controlled group did not (placebo not described). The description of the intervention for the included trial's is shown in [Appendix 2](#).

### Outcomes

The details of the outcomes are stated in the 'Characteristics of included studies' and [Appendix 4](#).

### Excluded studies

There were three studies excluded from the review. The reasons for exclusion were due to non-type 1 diabetes participants, non-HRT intervention used, or participants were not menopausal (see 'Characteristics of excluded studies').

### Risk of bias in included studies

For details on the methodological quality of the included study see 'Characteristics of included studies'.

### Effects of interventions

See: [Summary of findings for the main comparison](#)

### Baseline characteristics

For details of baseline characteristics, see [Appendix 3](#).

### Primary outcomes

No interaction between type of diabetes (T1DM or T2DM) and treatment (HRT or placebo) achieved statistical significance for any of the variables analysed. Study authors pooled all results by combining all diabetes participants. Diabetes and non-diabetes related morbidities and health-related quality of life were not investigated.

### Glycaemic control

Glycaemic control (measuring fructosamine) showed no statistically significant treatment effect ( $P = 0.27$ ) or effect of type of diabetes ( $P = 0.45$ ).

### Secondary outcomes

No interaction between type of diabetes (T1DM or T2DM) and treatment (HRT or placebo) achieved statistical significance for any of the variables analysed. Study authors pooled all results by combining all diabetes participants.

Death from any cause, frequency and severity of hypoglycaemia, body mass index, weight, total daily insulin dosage and economic data were not investigated.

### Adverse effects

HRT was associated with more adverse events: the most frequently reported event was breast pain (37 HRT T1DM and T2DM participants versus nine placebo participants); vaginal bleeding occurred in 26 HRT versus three placebo participants.

### Other outcomes

Other investigated outcomes of the included study were cardiovascular risk factors. Low-density lipoprotein (LDL) fell in both treatment groups. The difference between treatment groups was not significant (0.14 mmol/L; 95% CI -0.44 to +0.17;  $P = 0.37$ ). High-density lipoprotein (HDL) were significantly lower with HRT than placebo (-0.2; 95% CI -0.28 to -0.11;  $P < 0.001$ ). Sub-group analysis between T1DM and T2DM showed a decrease in mean HDL in T1DM only.

## DISCUSSION

### Summary of main results

The main finding from the single study (Scott 2004) identified through our search indicates that hormone replacement therapy (HRT) may not worsen glycaemic control in women with type 1 diabetes. This finding is in agreement with previous studies involving women who have type 2 diabetes (Crespo 2002; Ferrara 2001). However, there are limitations in the Scott 2004 study that must be considered. No pre- or post-intervention information regarding glycosylated haemoglobin A1c (HbA1c) change was provided, which presents a limitation if the effects of HRT and glycaemic control are to be understood. In addition, no information regarding insulin regimen was provided, nor was there any information

relating to the amount of exogenous insulin taken. Therefore, it is not clear if the study participants in Scott 2004 altered their insulin intake throughout the study.

The complexity surrounding HRT and its effects on many of the physiological responses in women with diabetes are considerable. For example, women with type 1 diabetes tend to experience symptoms of menopause earlier than women without diabetes, which can potentially lead to a reduction in reproductive years (Dorman 2001). Furthermore, menstrual irregularities are reported more frequently in women with type 1 diabetes than women without diabetes and they particularly appear to have difficulty in controlling blood glucose levels around the time of menstruation (Strotmeyer 2006). It is perhaps not surprising that as a consequence, due to the lack of empirical evidence detailing the effects of HRT on glycaemic control, evidence-based guidelines on how to manage glycaemia during the menopause for women with type 1 diabetes are unavailable.

Thus, information regarding how HRT affects glycaemic control in women with type 1 diabetes is unclear. Studies which have reported glycaemic effects are limited (Scott 2004) and are often hampered by small sample sizes (Dorman 2001).

The key finding of this review is that HRT does not appear to worsen glycaemic control in women with type 1 diabetes. However, as previously discussed, findings from that study must be taken with caution given the study limitations.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is currently a lack of evidence regarding the use of hormone replacement therapy amongst menopausal women with type 1 diabetes. HRT may impact upon glycaemic control and cardiovascular risk of women with type 1 diabetes but this review cannot make any recommendations for practice.

### Implications for research

Research to examine this topic needs to be undertaken to inform future practice. Randomised controlled trials to measure the impact of HRT on glycaemic control and cardiovascular risk factors in women with type 1 diabetes are possible. Descriptive and qualitative studies would be beneficial to examine the impact of HRT from the healthcare professional and patient perspectives.

## ACKNOWLEDGEMENTS

None.

## REFERENCES

### References to studies included in this review

#### Scott 2004 *{published and unpublished data}*

\* Scott AR, Dhindsa P, Forsyth J, Mansell P. Effect of hormone replacement therapy on cardiovascular risk factors in postmenopausal women with diabetes. *Diabetes, Obesity and Metabolism* 2004;**6**:16–22.

### References to studies excluded from this review

#### Brown 2001 *{published and unpublished data}*

Brown JS, Vittinghoff E, Kanaya AM, Agarwal SK, Hulley S, Foxman B. Urinary tract infections in post menopausal women: effect of hormone therapy and risk factors. *The American College of Obstetricians and Gynaecologists* 2001;**98** (6):1045–52.

#### Hayward 2001 *{published data only}*

Hayward CS, Samaras K, Campbell L, Kelly RP. Effect of combination hormone replacement therapy on ambulatory blood pressure and arterial stiffness in diabetic postmenopausal women. *American Journal of Hypertension* 2001;**14**(7):699–703.

#### Kanaya 2003 *{published data only}*

Kanaya AM, Herrington D, Vittinghoff E, Lin F, Grady D, Bittner V, et al. Glycaemic effects of postmenopausal hormone therapy: the heart and estrogen/progestin replacement therapy. *Annals of Internal Medicine* 2003;**138** (1):1–9.

### Additional references

#### Ajabor 1972

Ajabor LN, Tsai CC, Vela P, Yen SS. Effect of exogenous oestrogen on carbohydrate metabolism in post menopausal women. *American Journal of Obstetrics and Gynecology* 1972;**113**:453–61.

#### Andersson 2000

Andersson B. Hormone replacement therapy in post menopausal women with diabetes mellitus: a risk benefit assessment. *Drugs and Aging* 2000;**17**:399–410.

#### Beral 2003

Beral V and Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the million women study. *Lancet* 2003;**362**:419–27.

#### Brussaard 1992

Brussaard HE, Gevers-Leuven JA, Kluft C, Krans HM, van Duyvenvoorde W, Buytenhek R, et al. Effect of 17 beta-estradiol on plasma lipids and LDL oxidation in post-menopausal women with type 2 diabetes mellitus. *Arteriosclerosis, Thrombosis and Vascular Biology* 1997;**17**: 324–30.

#### Cagnacci 1992

Cagnacci A, Soldani R, Carriero PL. Effects of low doses of transdermal 17-estradiol on carbohydrate metabolism in post menopausal women. *Journal of Clinical and Endocrinological Metabolism* 1992;**74**:1396–400.

#### Crespo 2002

Crespo CJ, Smit E, Snelling A. Hormone replacement therapy and its relationship to lipid and glucose metabolism in diabetic and nondiabetic postmenopausal women: results from the Third National and Nutritional Survey (NHANES III). *Diabetes Care* 2002;**25**:1675–80.

#### Crook 1997

Crook D, Godsland I, Hull J, Stevenson JC. Hormone replacement therapy with dydrogesterone and 17b oestradiol: effects of serum lipoproteins and glucose tolerance during 24 months follow up. *British Journal of Obstetrics and Gynaecology* 1997;**104**:298–304.

#### Cushman 2004

Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, et al. Estrogen plus progestin and risk of venous thrombosis. *JAMA* 2004;**292**:1573–80.

#### Dahlgren 2006

Dahlgren J. Pregnancy and insulin resistance. *Metabolic Syndrome and Related Disorders* 2006;**4**(2):149–52.

#### DCCT 1993

Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *New England Journal of Medicine* 1993;**329**(14):977–85.

#### Diabetes UK 2006

Diabetes UK. Research Strategy. Diabetes UK, London 2006.

#### Dorman 2001

Dorman JS, Steenkiste AR, Foley TP. Menopause in type 1 diabetic women: is it premature?. *Diabetes* 2001;**50**(8): 1857–62.

#### Ferrara 2001

Ferrara A, Karter AJ, Ackerson LM. Hormone replacement therapy is associated with better glycaemic control in women with type 2 diabetes: the Northern California Kaiser Permanente Diabetes Registry. *Diabetes Care* 2001;**25**:1144–50.

#### Freeman 2007

Freeman EW, Sammel MD, Lin H, Gracia CR, Pien GW, Nelson DB, et al. Symptoms associated with menopausal transition and reproductive hormones in mid life women. *Obstetrics and Gynecology* 2007;**110**(2):230–42.

#### Higgins 2002

Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**:1539–58.

#### Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analysis. *BMJ* 2003;**327**: 557–60.

#### Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0

- [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).
- Hulley 2002**  
Hulley S, Furburg C, Barrett-Connor E, Cauley J, Grady D, Haskell W, et al for the HERS Research Group. Noncardiovascular disease outcomes during the 6.8 years of hormone therapy. *JAMA* 2002;**288**:58–66.
- International Menopause Society 2008**  
Pines A, Sturdee DW, Birkhäuser MH, de Villiers T, Naftolin F, Gompel A, et al for the International Menopause Society. HRT in the early menopause: scientific evidence and common perceptions. *Climacteric* 2008;**11**:267–72.
- Khoo 2005**  
Khoo CL, Perera M. Diabetes and the menopause. *Journal of the British Menopause Society* 2005;**11**(1):6–11.
- Klein 1999**  
Klein EK, Klein R, Moss SE. Mortality and hormone-related exposure in women with diabetes. *Diabetes Care* 1999;**22**(2):248–52.
- Lau 2006**  
Lau J, Ioannidis JPA, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. *BMJ* 2006;**333**:597–600.
- Liberati 2009**  
Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic and meta-analyses of studies that evaluate interventions: explanation and elaboration. *PLoS Medicine* 1999;**6**(7):1–28. [DOI: 10.1371/journal.pmed.1000100]
- Lindheim 1993**  
Lindheim SR, Presser SC, Ditkoff EC. A possible bimodal effect of oestrogen on insulin sensitivity in post menopausal women and the attenuating effect of added progestin. *Metabolism* 1993;**42**:664–7.
- MacLennan 2004**  
MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD002978.pub2]
- Million Women Study Collaborators 2007**  
Million Women Study Collaborators. Ovarian cancer and HRT in the million women study. *Lancet* 2007;**369**:1703–10.
- Norris 2001**  
Norris SL, Engelgau M, Nanayan KNV. Effectiveness of self-management training in type 2 diabetes: a systematic review of randomised control trials. *Diabetes Care* 2001;**4**(3):561–87.
- Progetto Menopausa Italia Study Group 2001**  
Progetto Menopausa Italia Study Group 2001. General and medical factors associated with hormone replacement therapy among women attending menopause clinics in Italy. *Menopause* 2001;**8**:290–5.
- Robinson 1996**  
Robinson JC, Folsom AR, Nabulsi AA, Watson R, Brancati FL, Cai J. Can postmenopausal hormone replacement improve plasma lipids in women with diabetes? The atherosclerosis risk in communities study investigators. *Diabetes Care* 1996;**19**:480–5.
- Rossouw 2007**  
Rossouw JE, Prentice RL, Manson JE, Wu LL, Barad D, Barnabei VM, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA* 2007;**297**:1465–77.
- Russel 2001**  
Russel E, Glasgow RE, Toobert DJ, Gillette CD. Psychosocial barriers to diabetes self-management and quality of life. *Diabetes Spectrum* 2001;**14**:33–41.
- Satter 1996**  
Satter N, Jaap AJ, MacCuish AC. Hormone replacement therapy and cardiovascular risk in post menopausal women with NIDDM. *Diabetic Medicine* 1996;**13**:782–8.
- Signuroardottir 2005**  
Signuroardottir AK. Self care in diabetes: models of factors affecting self care. *Journal of Clinical Nursing* 2005;**14**:301–14.
- Smith 2000**  
Smith MR, Feher MD. Hormone replacement therapy, cardiovascular risk factors and diabetes. *Journal of British Menopause Society* 2000;**6**(3):94–8.
- Sterne 2011**  
Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002.
- Strotmeyer 2006**  
Strotmeyer ES, Cauley JA, Orchard TJ. Middle-aged premenopausal women with type 1 diabetes have lower bone mineral density and calcaneal quantitative ultrasound than nondiabetic women. *Diabetes Care* 2006;**29**(2):306–11.
- Weinger 2001**  
Weinger K, Jacobson AM. Psychosocial and quality of life correlates of glycaemic control during intensive treatment of type 1 diabetes. *Patient Education and Counselling* 2001;**42**:123–31.
- Welton 2008**  
Welton AJ, Vickers MR, Kim J, Ford D, Lawton BA, MacLennan AH, et al. Health related quality of life after combined hormone replacement therapy: randomised control trial: one year's results of the women's international study of long duration oestrogen after menopause (WISDOM) trial. *BMJ* 2008;**337**:a1190.
- Women's Health Initiative Investigators 2002**  
Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principle results from the women's health initiative randomized control trial. *JAMA* 2002;**288**:321–33.



**Zarzycki 2005**

Zarzycki W, Zieniewick M. Reproductive disturbances in type 1 diabetic women. *Neuroendocrinology Letters* 2005;**26**(6):733–8.

\* *Indicates the major publication for the study*

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Scott 2004

Methods	Randomised controlled clinical trial
Participants	<p><b>Inclusion criteria:</b> postmenopausal women (amenorrhoeic for at least one year or were aged up to 53 years and been receiving HRT in the past for at least six months)</p> <p><b>Exclusion criteria:</b> uncontrolled hypertension (diastolic &gt; 100 mmHg), renal impairment (creatinine &gt; 150 <math>\mu</math>mol/L), previous malignancy, unstable angina, myocardial infarction previous six months, hysterectomy or a history of excess alcohol consumption or taking warfarin or drugs which may interfere with oestrogen metabolism</p> <p><b>Diagnostic criteria:</b> amenorrhoeic for at least one year or were aged up to 53 years and had been receiving HRT in the past for at least six months</p> <p><b>Co-morbidities:</b> not stated</p> <p><b>Co-medications:</b> not stated</p>
Interventions	<p><b>Number of study centres:</b> 11 centres nationwide</p> <p><b>Country/location:</b> UK</p> <p><b>Setting:</b> delivered by healthcare professionals from hospital diabetic clinics in the UK</p> <p><b>Intervention:</b> oestrogen (17<math>\beta</math>-oestradiol, 2 mg) and progesterone (norethisterone acetate, 1 mg)</p> <p><b>Control:</b> placebo (no details stated)</p> <p><b>Treatment before study:</b> participants had been receiving HRT in the past for at least six months</p>
Outcomes	<p><b>Outcome(s)</b> (as stated in the protocol/registered trial documents):</p> <p><b>Primary outcome(s):</b></p> <p>Total cholesterol (cholesterol oxidase fully enzymatic assay)</p> <p>LDL (polyethylene glycol (PEG) precipitation)</p> <p>HDL (polyethylene glycol (PEG) precipitation)</p> <p>Triglycerides (lipase/glycerol 3-phosphate oxidase assay)</p> <p>Fibrinogen (immunoturbidimetric assay)</p> <p>Body mass index (kg/m<sup>2</sup>)</p> <p>Blood pressure (mm Hg)</p> <p><b>Secondary outcomes:</b> not stated</p> <p><b>Additional outcomes:</b> not stated</p>
Study details	After a 6-week run-in period, the study lasted for 12 months
Publication details	<b>This study was commercially funded</b>
Stated aim of study	"...was to examine the effects of HRT (Kliofem) on cardiovascular risk factors, including lipid profile, glycaemic control, blood pressure and body weight, in postmenopausal women with T1DM or T2DM"
Notes	Key findings: this study demonstrates that HRT results exert a minimal effect on glycaemic control. In relation to cardiovascular risk factors, HRT appears to have a neutral effect on most, though the effects on HDL warrants further investigation

	Quote from publication: “None of the interactions between type of diabetes (T1DM or T2DM) and treatment (Kliofem/placebo) achieved statistical significance for any of the variables analysed; hence, all results are reported for the total number of diabetics completing the study”	
<i><b>Risk of bias</b></i>		
<b>Bias</b>	<b>Authors’ judgement</b>	<b>Support for judgement</b>
Allocation concealment (selection bias)	Unclear risk	Comment: method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Comment: no information on blinding method is given.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: “Variables missing values for the 52-week visit were replaced using the last observation carried forward technique ... Where week 0 values were missing, they were replaced by the week -6 values”
Selective reporting (reporting bias)	Low risk	Comment: all of the study’s outcomes have been reported
Other bias	High risk	Quote: “55 patients withdrew from the study... main reasons were adverse effects or persistence of menopausal symptoms” Comment: no information is provided detailing the differences in drop-out rate between type 1 diabetes mellitus and type 2 diabetes mellitus

HDL: high-density lipoprotein; HRT: hormone replacement therapy; LDL: low-density lipoprotein

### Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brown 2001	Not type 1 diabetes participants
Hayward 2001	Not type 1 diabetes participants
Kanaya 2003	Not type 1 diabetes participants

## DATA AND ANALYSES

This review has no analyses.

## ADDITIONAL TABLES

Table 1. Overview of study populations

Characteristic Study ID	Intervention (s) and comparator (s)	[N] screened / eligible	[N] randomised	[N] safety	[N] ITT	[N] finishing study	[%] randomised participants finishing study
Scott 2004 <sup>a</sup>	Hormone replacement therapy vs placebo	I: 27 C: 29 T: 56	I: 27 C: 29 T: 56	-	-	-	N/A
<i>Total</i>	<i>All interventions</i>		27				
	<i>All controls</i>		29				
	<i>All interventions and controls</i>		56				

“-” denotes not reported

<sup>a</sup>Data on drop-outs, losses to follow-up and missing data were not reported in the type 1 diabetes mellitus participants

C: comparator; I: intervention; N/A: not applicable

## APPENDICES

### Appendix I. Search strategies

Search terms and databases
<p>Unless otherwise stated, search terms are free text terms.</p> <p>Abbreviations:</p> <p>'\$': stands for any character; '?': substitutes one or no character; adj: adjacent (i.e. number of words within range of search term); exp: exploded MeSH; MeSH: medical subject heading (MEDLINE medical index term); pt: publication type; sh: MeSH; tw: text word</p>
<i>The Cochrane Library</i>

(Continued)

### ***The Cochrane Library***

- #1 MeSH descriptor Diabetes mellitus, type 1 explode all trees
- #2 MeSH descriptor Diabetic Ketoacidosis explode all trees
- #3 MeSH descriptor Diabetes Complications explode all trees
- #4 (IDDM in All Text or T1DM in All Text)
- #5 ((insulin\* in All Text and depend\* in All Text) or insulin?depend\* in All Text)
- #6 (typ\* in All Text and 1 in All Text and adj6 in All Text and diabet\* in All Text)
- #7 (earl\* in All Text and adj6 in All Text and diabet\* in All Text)
- #8 (auto?immun\* in All Text and adj6 in All Text and diabet\* in All Text)
- #9 ((sudden in All Text and onset in All Text) and adj6 in All Text and diabet\* in All Text)
- #10 (insulin\* in All Text and defic\* in All Text and adj6 in All Text and absolut\* in All Text)
- #11 (acidos\* in All Text and adj6 in All Text and diabet\* in All Text)
- #12 (juvenil\* in All Text and adj6 in All Text and diabet\* in All Text)
- #13 (child\* in All Text and adj6 in All Text and diabet\* in All Text)
- #14 (keto\* in All Text and adj6 in All Text and diabet\* in All Text)
- #15 (labil\* in All Text and adj6 in All Text and diabet\* in All Text)
- #16 (britt\* in All Text and adj6 in All Text and diabet\* in All Text)
- #17 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)
- #18 MeSH descriptor Diabetes insipidus explode all trees
- #19 (diabet\* in All Text and insipidus in All Text)
- #20 (#18 or #19)
- #21 (#17 and not #20)
- #22 MeSH descriptor Hormone replacement therapy explode all trees
- #23 (hormon\* in All Text and (replacement in All Text AND therap\* in All Text) )
- #24 (hormon\* in All Text and (replacement in All Text AND intervention\* in All Text) )
- #25 (#22 or #23 or #24)
- #26 #21 and #25

### **MEDLINE**

- 1. exp Diabetes Mellitus, Type 1/
- 2. exp Diabetic Ketoacidosis/
- 3. exp Diabetes Complications/
- 4. (IDDM or T1DM or T1D).tw,ot.
- 5. (((“insulin\* depend\*” or “insulin?depend\*”) not (“non-insulin\* depend\*” or “noninsulindepend\*”)).tw,ot.
- 6. (((“typ? 1” or “typ? I” or “typ?1” or “typ?I”) adj2 diabet\*).tw,ot.
- 7. ((acidos\* or juvenil\* or child\* or keto\* or labil\* or britt\*) adj2 diabet\*).tw,ot.
- 8. ((auto-immun\* or autoimmun\* or sudden onset) adj2 diabet\*).tw,ot.
- 9. (insulin\* defic\* adj2 absolut\*).tw,ot.
- 10. or/1-9
- 11. exp Diabetes Insipidus/
- 12. diabet\* insipidus.tw,ot.
- 13. 11 or 12
- 14. 10 not 13
- 15. exp Hormone Replacement Therapy/
- 16. hormone replacement\*.tw,ot.
- 17. or/15-16
- 18. 14 and 17
- 19. (animals not (animals and humans)).sh.

(Continued)

20. 17 not 18
21. Limit 20 to RCT

---

#### EMBASE

---

1. exp Insulin Dependent Diabetes Mellitus/
2. exp Diabetic Ketoacidosis/
3. exp Diabetic Retinopathy/ or exp Diabetic Angiopathy/ or exp Diabetic Neuropathy/ or
4. exp Diabetic Nephropathy/
5. (IDDM or T1DM).tw,ot.
6. (insulin\$ depend\$ or insulin?depend\$).tw,ot.
7. ((typ\$ 1 or typ\$I) adj6 diabet\$).tw,ot.
8. ((earl\$ or auto?immun\$ or sudden onset) adj6 diabet\$).tw,ot.
9. (insulin\$ defic\$ adj6 absolut\$).tw,ot.
10. ((acidosis\$ or juvenil\$ or child\$ or keto\$ or labil\$ or britt\$) adj6 diabet\$).tw,ot
11. or/1-9
12. exp Diabetes Insipidus/
13. diabet\$ insipidus.tw,ot.
14. 11 or 12
15. 10 not 13
16. exp hormone substitution/
17. (hormon\* adj3 (substitution\* or replacement\*)).tw,ot.
18. or/15-16
19. 14 and 17
20. limit 18 to human
21. limit 19 to RCT

---

#### CINAHL

---

1. (MH "Diabetes Mellitus, Type 1")
2. (MH "Diabetic Ketoacidosis")
3. Diabetes Complications/
4. (IDDM or T1DM or T1D).tw,ot.
5. ((("insulin\* depend\*" or "insulin?depend\*") not ("non-insulin\* depend\*" or "non insulindepend\*"))).tw,ot.
6. ((("typ? 1" or "typ? I" or "typ?1" or "typ?I") adj2 diabet\*).tw,ot.
7. ((acidosis\* or juvenil\* or child\* or keto\* or labil\* or britt\*) adj2 diabet\*).tw,ot.
8. ((auto-immun\* or autoimmun\* or sudden onset) adj2 diabet\*).tw,ot.
9. (insulin\* defic\* adj2 absolut\*).tw,ot.
10. or/1-9
11. exp Diabetes Insipidus/
12. diabet\* insipidus.tw,ot.
13. 11 or 12
14. 10 not 13
15. exp Hormone Replacement Therapy/
16. hormone replacement\*.tw,ot.
17. exp Menopause, Premature/ or exp Menopause/
18. (menopaus\$ or postmenopaus\$ or perimenopaus\$ or premenopaus\$).tw,ot.
19. or/15-18
20. 14 and 19
21. limit 18 to female

(Continued)

22. (animals not (animals and humans)).sh.  
23. 19 not 20

## PsycINFO

1. (TX+(Diabetes+Mellitus))+OR+(TX+(Type+1)))
2. (TX+(Diabetic+Ketoacidosis))
3. (TX+(Diabetes+Complications))
4. (TX+(IDDM))+OR+(TX+(T1DM))
5. ((TX+(insulin\*+AND+depend\*))+OR+(TX+(insulin%3fdepend\*)))
6. ((TX+(typ\*))+AND+1+AND+adj6+AND+diabet\*))+OR+((TX+(earl\*))+AND+TX+(adj6)+AND+TX+(diabet\*)))
7. ((TX+(auto%3fimmun\*))+AND+(TX+(adj6))+AND+(TX+(diabet\*)))
8. ((TX+(sudden+AND+onset))+AND+(TX+(adj6))+AND+(TX+(diabet\*)))
9. ((TX+(insulin\*))+AND+(TX+(defic\*))+AND+(TX+(adj6))+AND+(TX+(absolut\*)))
10. ((TX+(acidosis\*))+AND+(TX+(adj6))+AND+(TX+(diabet\*)))
11. ((TX+(juvenil\*))+AND+(TX+(adj6))+AND+(TX+(diabet\*)))
12. ((TX+(child\*))+AND+(TX+(adj6))+AND+(TX+(diabet\*)))
13. ((TX+(keto\*))+AND+(TX+(adj6))+AND+(TX+(diabet\*)))
14. ((TX+(labil\*))+AND+(TX+(adj6))+AND+(TX+(diabet\*)))
15. ((TX+(britt\*))+AND+(TX+(adj6))+AND+(TX+(diabet\*)))
16. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
17. (TX+(diabetes+insipidus))
18. ((TX+(diabet\*))+AND+(TX+(insipidus))))))
19. S17 OR S18
20. S16 NOT S19
21. (((MJ+(Hormone+Replacement+Therapy))))
22. ((TX+(hormon\*+AND+replacement+AND+therap\*)))
23. ((TX+(hormon\*+AND+replacement+AND+intervention\*))))))
24. S21 OR S22 OR S23
25. S20 AND S24

## Appendix 2. Description of interventions

Characteristic Study ID	Intervention [route, frequency, total dose/day]	Comparator [route, frequency, total dose/day]
Scott 2004	Hormone replacement therapy (oestrogen (17B-oestradiol, 2 mg) and progesterone (norethisterone acetate, 1 mg))	Placebo (not described)

### Appendix 3. Baseline characteristics

Characteristic Study ID	Duration of intervention (duration of follow-up)	Participating population	Age [mean years (SD)]	HbA1c [mean % (SD)]	BMI [mean kg/m <sup>2</sup> (SD)]	Ethnic groups [%]	Duration of disease [mean years (SD)]
Scott 2004	12 months (at 12 months)	55	60 (6)	-	28.5 (6.1)	-	-
<i>Footnotes</i> “-” denotes not reported BMI: body mass index; HbA1c: glycosylated haemoglobin A1c; SD: standard deviation							

### Appendix 4. Matrix of study endpoints

Characteristic	Primary <sup>a</sup> endpoint(s)	Secondary <sup>b</sup> endpoint(s)	Other <sup>c</sup> endpoint(s)
Scott 2004	Cardiovascular risk factors (lipid profile), glycaemic control (fructosamine), blood pressure, BMI	-	-
<i>Footnotes</i> <sup>a,b</sup> as stated in the publication; <sup>c</sup> not stated as primary or secondary endpoint(s) in the publication BMI: body mass index			

### Appendix 5. Adverse events (I)

Characteristic Study ID	Deaths [n]	Adverse events [n / %]	Severe/ serious adverse events [n / %]	Drop-outs due to adverse events [n / %]	Hospitalisa- tion [n / %]	Out-patient treatment [n / %]	Hypogly- caemic episodes [n / %]
Scott 2004	-	-	-	-	-	-	-
<i>Footnotes</i> “-” denotes not reported							



## Appendix 6. Adverse events (II)

Characteristic Study ID	Severe hypoglycaemic episodes [n / %]	Definition of severe / serious hypoglycaemia	Nocturnal hypoglycaemic episodes [n / %]	Symptoms [n / %]
Scott 2004	-	-	-	-
<i>Footnotes</i> “-” denotes not reported				

## CONTRIBUTIONS OF AUTHORS

Liz Mackay (LM): drafted the protocol, developed a search strategy, searched for trials, obtained copies of trials, selected which trials to include, extracted data from trials, entered data into RevMan, carried out the analysis, interpreted the analysis, drafted the final review and will update the review when necessary.

Lynn Kilbride (LK): drafted the protocol, developed a search strategy, searched for trials, obtained copies of trials, selected which trials to include, extracted data from trials, entered data into RevMan, carried out the analysis, interpreted the analysis, drafted the final review and will update the review when necessary.

Karen A Adamson KA): drafted the protocol, searched for trials, selected which trials to include, extracted data from trials, carried out the analysis, interpreted the analysis, drafted the final review and will update the review when necessary.

John Chisholm (JC): drafted the protocol, developed a search strategy, searched for trials, obtained copies of trials, selected which trials to include, extracted data from trials, entered data into RevMan, carried out the analysis, interpreted the analysis, drafted the final review and will update the review when necessary.

## DECLARATIONS OF INTEREST

None known.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Blood Glucose; Diabetes Mellitus, Type 1 [blood; \*drug therapy]; Diabetes Mellitus, Type 2 [blood; drug therapy]; Estradiol [administration & dosage]; Estrogen Replacement Therapy [\*methods]; Norethindrone [administration & dosage; analogs & derivatives]; Postmenopause [drug effects; physiology]; Randomized Controlled Trials as Topic; Risk Factors

## MeSH check words

Female; Humans